

# Cardiovascular medication in women and continence

Urinary continence in women is subject to many influences, not least age, obesity, diabetes and parity. In addition, several drugs used in cardiovascular medicine have the potential to affect continence. Women should be sympathetically questioned with regard to urinary continence prior to prescribing cardiac medications and counselled regarding potential effects.

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Many cardiovascular medications have the potential to affect the function of the female bladder and urinary tract. The prevalence of urinary incontinence (UI) in women rises steadily from age 15 years onwards,<sup>1</sup> with estimates for the general population of between 12–51%,<sup>2–5</sup> to rates reaching 52% in women over 70,<sup>6,7</sup> and 56% in women over 80 years of age.<sup>8</sup>

We describe the apparent influence of cardioactive medications, age, diabetes and race on aspects of urinary incontinence in women.

## Methods

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Women attending cardiology out-patient clinics, at two west London district general hospitals, with a diagnosis of hypertension were questioned. Age, race, diabetes and cardio-active medications were recorded for their effects on UI. Patients with a high requirement for diuretics (>80mg of frusemide or equivalent), were excluded.

Urinary incontinence was defined as any involuntary loss of urine within the last three months. Patients were asked the question, "do you have any problems with the 'water-works'?" More directed enquiry asked five further specific questions concerning "stress", "urgency" or "total" incontinence, "nocturia" and the use of any sanitary (incontinence) precautions.

"Total" incontinence was defined as UI occurring "without control and at any time"; nocturia as >2

voiding episodes per night.<sup>9</sup> "Any" UI was defined as either stress or urgency incontinence; mixed UI as both stress and urge UI. Data on continence was collected through a reproducible systematic approach using five ordered questions on a schematic diagram in patients records, to indicate responses.

## Analysis

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Of 1,175 patients sampled, six were unable to fully comprehend the questions and were excluded. Multivariate logistic regression analyses were performed on those variables that showed some association ( $p < 0.2$ ) with outcomes of urinary continence on an initial univariate analysis. Age was considered on a continuous scale, with odds ratios reflecting an effect of age upon the odds of urinary continence, for any 10 year increment in age. A Chi-square test was used to examine associations for variables between groups of patients.

## Results

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1169 women were audited between August 2008 and September 2010. Their mean ( $\pm$ SD, median, range) age was 68 ( $\pm$ 14, 71, 21–97) years. 66% were aged of >65 years of age (mean 76, range 65–97 years), 44% were of <65 years of age and 11% were <50 years of age. 928 were Caucasian (80.0%); 204 Asian (17.5%), 30

Afro-Caribbean (2.5%) and 12 of other races. Diabetes was recorded in 220 (18.8%) and 25 women (2.2%) were markedly obese (BMI>30 kg/m<sup>2</sup>).

Twenty eight (2.4%) patients had previously, or were still taking medication for UI. 27 (2.3%) women had undergone reparative bladder surgery and 11 women (0.9%) were prescribed a vaginal ring pessary.

Overall, 396 women (34%) actively volunteered issues with UI. On direct inquiry a total of 686 (59%) admitted to some degree of "any" UI in the preceding three months and 381 (33%) used some form of sanitary protection.

## Cardio-active medications and features of urinary incontinence

Many patients (56%) were taking more than one anti-hypertensive medication. We focused the analyses on two specific categories of UI; namely "any" UI and nocturia.

### "Any" urinary incontinence

When medications were considered individually, there was a significant association (Odds ratio, 95% CI, p value) for an increase in "any" UI with both angiotensin II blockers (1.43, 1.09–1.87, p=0.009) and alpha blockers (1.53, 1.04–2.25, p=0.03). In contrast, aldosterone antagonists demonstrated a negative association with UI (0.5, 0.29–0.85, p=0.01). Patients on no medication showed a possible trend for a lower occurrence of "any" UI (0.71, 0.49–1.03, p=0.07).

On multivariate analysis, only angiotensin II blockers retained a significant association with an increase in "any" UI (1.43, 1.09–1.88, p=0.01). Aldosterone antagonists continued to demonstrate a significant reduction in "any" UI (0.47, 0.28–0.81, p=0.006). After adjusting for all variables there was no apparent effect of alpha blockers upon the occurrence of "any" UI.

### Nocturia

Calcium channel blockers and alpha blockers were significantly associated, on univariate analysis, with an increase in nocturia (Odds ratio 1.91, 1.49–2.43, p<0.001 and 1.61, 1.12–2.32, p=0.01 respectively). Women receiving no cardiovascular medication had less nocturia (0.37, 0.24–0.57, p<0.001).

On multivariate analysis, calcium channel blockers retained their significant association with nocturia (1.6, 1.24–2.07, <0.001) as did no cardiovascular medication with less nocturia (0.52, 0.33–0.82, p=0.005). In contrast the relationship between alpha blockers and nocturia was no longer apparent.

### The influence of age, race, and diabetes

In older women (>65 years of age), 58.7% reported the occurrence of "any" UI, compared with 57.9% of women aged less than 65. Nocturia was reported by 43.4% of older women compared with 37.7% of those under 65 (p=0.05). An increment of 10 years in age was associated with a 15% increase in odds for nocturia (Odds ratio 1.15, 1.06–1.26, p=0.002). Older women also used more sanitary protection than younger women (35.4% versus 26.9% respectively, p=0.004); although the prevalence of "total" incontinence between older women and younger women did not achieve significance (3.4% versus 2.0%, p=0.19).

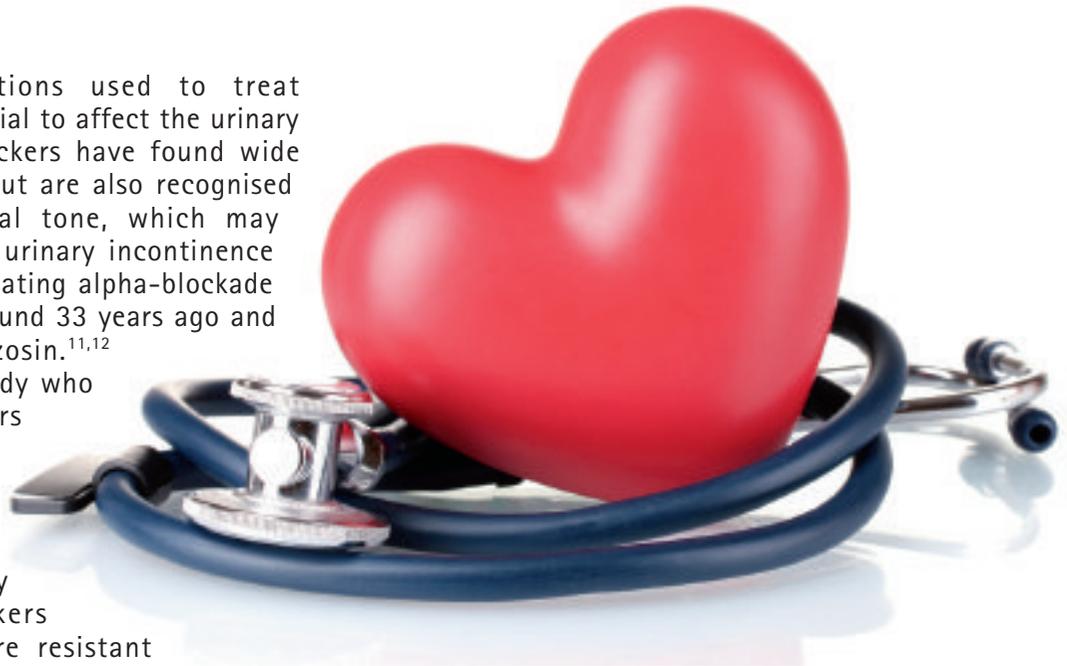
There was a trend to more Caucasian women volunteering that "the waterworks were OK" than did Asian women (29.8% versus 24.0%, p=0.07). In contrast, more Caucasians volunteered actual UI than did Asian women (34.5% versus 27.5%, p=0.08). On direct enquiry, Asian women reported a similar prevalence of UI of "any" type, compared with Caucasian (56% versus 59%, p=0.36).

Overall, women with diabetes were of a similar age as non-diabetic women at 68 years, but were taking more cardioactive medications than non diabetic women (2.43 versus 1.65 drugs per patient) respectively. More diabetic women reported the occurrence of "any" UI than did non-diabetics (65.6% versus 56.8%: Odds ratio of 1.46, 1.07–1.98, p=0.02), more nocturia (55.7% versus 38.1%, Odds ratio 2.04, 1.51–2.74, p<0.001) and also had a higher prevalence of total UI (4.5% versus 2.5%).

## Discussion

The overwhelming observation from this study is that UI is highly prevalent in women within the age range studied. Of this relatively large sample of female patients, more than half (59%) reported some issues with continence. It was also apparent that those receiving no cardioactive medications were less likely to suffer "any" UI and had significantly less nocturia.

Many of the medications used to treat hypertension have the potential to affect the urinary system (Table 1). Alpha-blockers have found wide use as anti-hypertensive,<sup>10</sup> but are also recognised to cause a loss of urethral tone, which may predispose women to stress urinary incontinence in women.<sup>11-14</sup> Reports associating alpha-blockade with UI began to emerge around 33 years ago and concerned the use of prazosin.<sup>11,12</sup> However, patients in our study who were prescribed  $\alpha$ -blockers were also taking on average 3.1 anti-hypertensive drugs (whereas, the overall study average was 1.8 medications). This is probably indicative of alpha-blockers being co-prescribed in more resistant cases. Patients on alpha-blockers also tended to be older, on average by a year (69+11, median 70 years) than those not taking alpha-blockers (68+14, median 71 years) and were more likely to be diabetic (28.2% versus 17.6%). In consequence, their effect on "any"



UI was not evident after adjustment for all these variables. Paradoxically, alpha-blockers have been used as a treatment for urgency incontinence.<sup>15-17</sup> Opinion on the use of alpha blockers appears divided, particularly as a recent large randomised double-blind clinical trial showed no benefit for the alpha-blocker tamsulosin when compared with placebo in 364 women with overactive bladder symptoms.<sup>18</sup>

Somewhat unexpectedly, angiotensin-II blockers demonstrated a significantly adverse effect on "any" UI and aldosterone antagonists a beneficial association. Although studies in humans are limited, it is established that the bladder has angiotensin I and II receptors which, in the case of angiotensin II, exerts a potent influence on detrusor muscle contraction.<sup>19</sup> In rats angiotensin II appears to serve a functional role in the maintenance of urethral tone;<sup>20</sup> whether this translates to an effect on UI in humans with the use of angiotensin-II blockers is not established.

Calcium channel blockers had the greatest influence on nocturia, likely due to their potential to cause fluid retention (Table 1). This result was not unexpected with a recognised side effect profile including frequency of micturition, polyuria and nocturia for this class of drugs.<sup>21</sup> In the case of "total" incontinence, the apparently high prevalence with centrally acting drugs may have been influenced by the relatively small number of patients (n=14) taking these drugs, the high total number of cardioactive drugs taken by these patients (3.9 drugs/patient) and/

**Table 1:** Cardio-active medications with potential effects on female continence

Cardioactive medications	Potential effects on urinary continence
ACE inhibitors	Cough, <sup>21</sup> causing "stress" incontinence.
Calcium channel blockers	Fluid retention, <sup>21</sup> may exacerbate "nocturia".
Diuretics (Loop diuretics, thiazides and aldosterone antagonists)	"Urge" incontinence. <sup>21</sup>
Alpha blockers	Effects may cause/exacerbate incontinence, <sup>21</sup> influencing both "stress" and "urge" pattern.
Centrally acting agents	Limited influence aside from fluid retention with Methyl dopa, <sup>21</sup> might exacerbate "nocturia".

or a high prevalence of diabetes (35.7%).

As previously reported,<sup>22,23</sup> stress UI was the most frequently reported form of UI (43%) in women, followed by urgency incontinence (38%) and a smaller number with a mixed picture. This pattern is frequently adversely influenced by diabetes, body mass index and prior pregnancy,<sup>5,24-27</sup> irrespective of mode of delivery.<sup>25,28</sup>

The finding of less UI in Asian women than Caucasian was surprising. Asian women had higher parity than Caucasians (2.82 versus 2.15 children per woman), more were diabetic (36.3 versus 14.6%), more cardiac medications were prescribed (2.01 versus 1.72 drugs/patient) and a marginally higher proportion were markedly obese (2.4 versus 2.2%).

Previously, a large European survey reported that many women put off seeking advice about UI for many years. Of 9,000 women, 13% waited 6–10 years and 11% waited for 11 or more years.<sup>26</sup> Explanations include embarrassment, stigma, an "acceptance" that this is a natural consequence of age, parity or a combination.<sup>29</sup> This acceptance might also be reinforced by the current proliferation of television and magazine advertisements for sanitary protection.

Few patients in the study we describe were taking medication or had undergone interventions to prevent UI. We suggest under-reporting of symptoms and or acceptance of UI are both contributory.

### Limitations to the study

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The number of categories of anti-hypertensive agents, the use of combination therapies in 88.5% and the high background level of UI, may have contributed to a failure to detect statistically significant influences for some medications. The study is not powered to include the effects of the type of cardiovascular disease or other comorbidities on UI. This audit relied on patients recall of their symptoms and did not use the now recommended frequency/volume voiding charts, often completed over a three day time period.<sup>30</sup>

### Conclusion

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Urinary incontinence has a high prevalence in women, particularly at an age when there is substantial benefit from treatment of hypertension.<sup>31-34</sup> From all ages after 31 years, women form the majority of the UK

population, a proportion that increases dramatically in the age range of our patients.<sup>35,36</sup>

The influence of cardioactive medications on female urinary continence should therefore be recognised in much the same way as attention is paid to men, with regard to their prostate or sexual function and cardioactive medications. Women being prescribed these medications should be appropriately counselled on the potential effects these drugs may have on urinary continence.

Conflict of interest: none declared

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